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The first enantioselective synthesis of the amino acid, (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine using a palladium(II) catalysed 3,3-sigmatropic rearrangement

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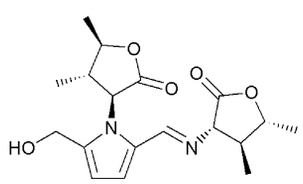
A synthetic route towards the synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine, the amino acid component of the natural product, funebrine has been developed using as the key step, a palladium(II) catalysed 3,3-sigmatropic rearrangement to create the (2*S*)-stereogenic centre.

The Zapotec tribes of southeastern Mexico accorded particular cultural significance to the tree, *Quararibea funebris* (Llave) Vischer (Bombacaceae). As well as conducting funeral rites beneath its branches, the plant was used as a cough remedy, an antipyretic, and to control menstrual disorders and psychopathic fears.[1] Investigation of the natural products contained within the flowers identified a series of compounds, including the novel pyrrole alkaloid, funebrine **1**.[2] Also isolated was the amino acid component of **1**, (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2**.



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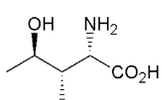
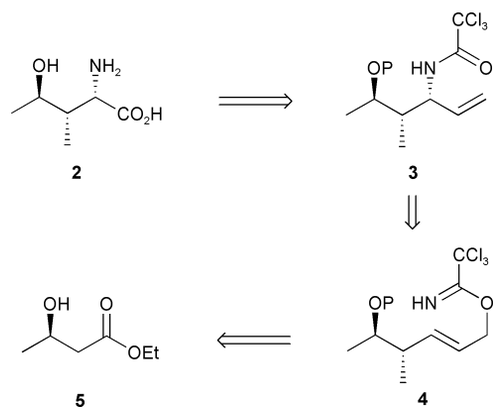


2

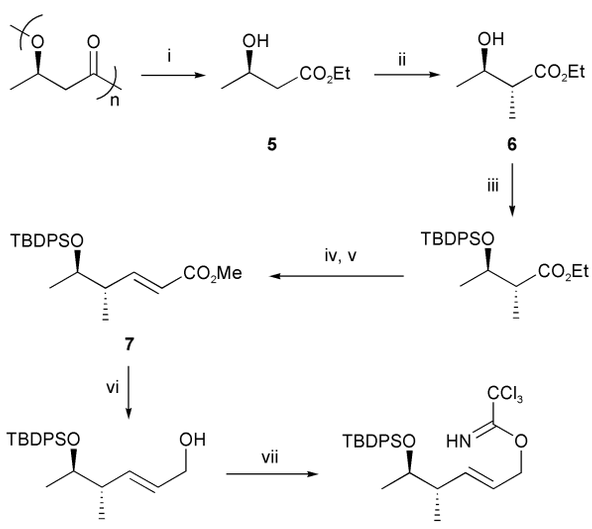
Other stereoisomers of γ-hydroxyisoleucine have been isolated from organisms such as *Trigonella foenum-graecum* (Leguminosae)[3] and *Amanita phalloides*,[4] and this has led to the development of methodology towards the synthesis of these isomers of the amino acid.[5] Le Quesne and co-workers completed the first total synthesis and conformational studies of (±)-funebrine.[6] However, as yet, there is no reported synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2**. Recently we initiated a research programme to investigate 3,3-sigmatropic rearrangements of chiral molecules. We now report the first enantioselective synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2** using allylic 1,3-strain to control the stereoselectivity in the key step, which involves a palladium(II) catalysed 3,3-sigmatropic rearrangement.

Our retrosynthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2** is shown in Scheme 1. The key intermediate, trichloroacetimidate **4** was to be prepared from readily available ethyl (*R*)-hydroxybutanoate **5**. Stereoselective rearrangement of **4** would then allow the formation of the allylic trichloroamide **3** introducing the (2*S*)-stereogenic centre. Finally, oxidative cleavage of the alkene and deprotection would give the target amino acid.

The first stage of the synthesis involved the preparation of the trichloroacetimidate **9** (Scheme 2). Acid hydrolysis of poly (*R*)-hydroxybutanoate gave ethyl (*R*)-hydroxybutanoate **5**[7] and this was used to install the (3*S*)-stereogenic centre of the target amino acid using a stereoselective alkylation. Treatment of **5** with two equivalents of LDA forms a di-lithiated chair-like enolate which undergoes alkylation from the least hindered face



Scheme 1



Scheme 2 *Reagents and conditions*: i. H_2SO_4, $ClCH_2CH_2Cl$, EtOH, Δ, 82%; ii. LDA (2 equiv.), MeI, THF, −78 °C, 84%; iii. TBDPSCl, imidazole, THF, 96%; iv. DIBAL-H, Et_2O, −78 °C, 94%; v. $Ph_3P{=}CHCO_2Me$, THF, 90%; vi. DIBAL-H (2.2 equiv.), Et_2O, −78 °C, 89%; vii. NaH, Cl_3CCN, 0 °C, 83%.

to give the *erythro* product **6**.[8] Protection of the hydroxyl group as the TBDPS silyl ether followed by reduction of the ester to the aldehyde and subsequent coupling with the stabilized ylide, methyl (triphenylphosphoranylidene)acetate gave solely the *trans*-alkene **7** in excellent yield. Reduction of **7** with DIBAL-H afforded (2*E*,4*S*,5*R*)-allylic alcohol **8** in 5 steps and 61% overall yield from ethyl (*R*)-3-hydroxybutanoate **5**. Alcohol **8** was converted to the trichloroacetimidate **9** using sodium hydride and trichloroacetonitrile.[9]

The next stage was to investigate the proposed 3,3-sigmatropic rearrangement to introduce the (2*S*)-stereogenic centre

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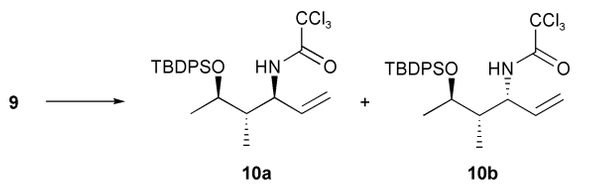
Table 1 Rearrangement of trichloroacetimidate **9**



Entry	Conditions	Ratio (**10a** : **10b**)	Yield (%)
1	*p*-xylene, Δ, 24 h	3 : 2	54
2	$PdCl_2[MeCN]_2$, r.t., 3 h	1 : 6	65
3	$PdCl_2[PhCN]_2$, r.t., 3 h	1 : 7	71

of the amino acid. We initially carried out a thermal rearrangement using Overman conditions in refluxing *p*-xylene (Table 1).[10a] This gave the two diastereomeric rearranged products **10a** and **10b** in a very modest 3 : 2 ratio (entry 1). More importantly the major product was the unwanted (3*R*)-isomer. However, treatment of trichloroacetimidate **9** with either bis(acetonitrile)- or bis(benzonitrile)palladium(II) catalysts [10b] at room temperature (entries 2 and 3) led to a complete reversal in the stereochemical outcome of the reaction to give the desired (3*S*)-isomer as the major product.[11]

The stereoselectivity of both the thermal and the palladium catalysed rearrangement can be explained by considering the transition states (Fig. 1). In both cases a chair-like transition state is formed in which allylic 1,3-strain is minimised.[12] This causes the bulky TBDPS containing side chain to block the back face of the alkene and thus, during the thermal rearrangement, intramolecular attack by the trichloroacetimidate nitrogen occurs at the least hindered face of the alkene to give predominantly the (3*R*)-isomer. Alternatively, during the palladium catalysed reaction, initial coordination of the catalyst to the least hindered face of the alkene effectively blocks this side. Hence, intramolecular attack of the trichloroacetimidate nitrogen has to now take place from the back face of the alkene giving rise to the desired (3*S*)-isomer as the major product.

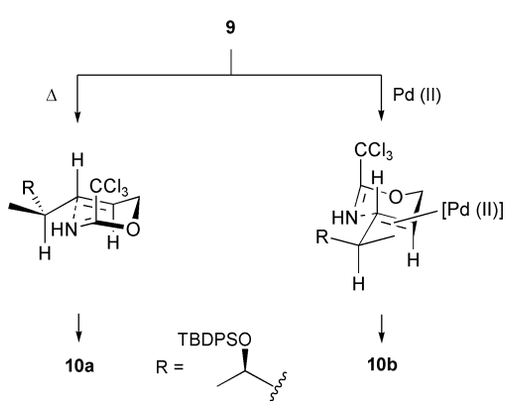
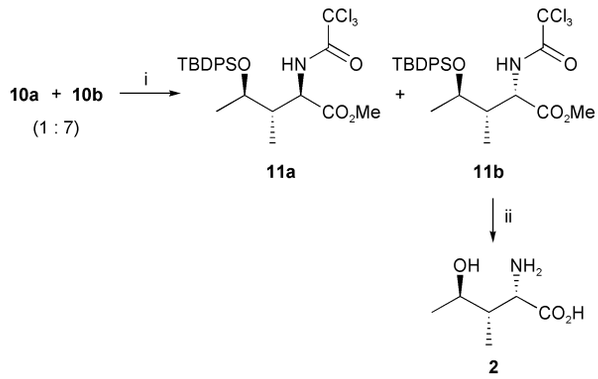


Fig. 1 Transition states for the thermal and palladium catalysed rearrangement of **9**.

The 7 : 1 mixture of diastereomers obtained from the bis(benzonitrile)palladium(II) catalysed reaction was elaborated to (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2** (Scheme 3). Oxidative cleavage of **10a** and **10b** in the presence of methanolic NaOH gave the corresponding methyl esters **11a** and **11b** in 74% yield.[13] At this stage the two diastereomers were separated using column chromatography. Deprotection of the major (2*S*)-isomer under acidic conditions followed by purification with ion exchange chromatography gave (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2** in 88% yield. Spectroscopic data was entirely consistent with that published for the natural product [2] thereby confirming our stereochemical assignment of the rearrangement products **10a** and **10b**.



Scheme 3 *Reagents and conditions*: i. O_3, NaOH, MeOH, −78 °C, 74%; ii. 6 M HCl, Δ, 24 h, 88%.

In conclusion, the first enantioselective synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **2** by consecutive introduction of the (3*S*)- and (2*S*)-stereogenic centres respectively has been accomplished in 10 steps and in 19.3% overall yield from poly (*R*)-hydroxybutanoate. We have previously reported an efficient synthesis of the enantiomer of allylic alcohol **8** in which a stereocontrolled aldol reaction of propionyl camphorsultam with acetaldehyde was used to create the stereogenic centres.[14] Hence the approach described herein may be readily adapted for the synthesis of (2*R*,3*R*,4*S*)-γ-hydroxyisoleucine. Further studies on the 3,3-sigmatropic rearrangement of chiral molecules for natural product synthesis are currently in progress.

Acknowledgements

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Notes and references

1 R. E. Schultes, *Bot. Mus. Leafl., Harv. Univ.*, 1957, **17**, 247.
2 R. F. Raffauf, T. M. Zennie, K. D. Onan and P. W. Le Quesne, *J. Org. Chem.*, 1984, **49**, 2714.
3 L. Fowden, H. M. Pratt and A. Smith, *Phytochemistry*, 1973, **12**, 1707.
4 A. Gieren, P. Narayanan, W. Hoppe, M. Hasan, K. Michl, T. Wieland, H. O. Smith, G. Jung and E. Breitmaier, *Justus Liebigs Ann. Chem.*, 1974, 1561.
5 For example see: Q. Wang, J. Ouazzani, N. A. Sasaki and P. Potier, *Eur. J. Org. Chem.*, 2002, 834; T. Kassem, J. Wehbe, V. Rolland-Fulcrand, M. Roland, M.-L. Roumestant and J. Martinez, *Tetrahedron: Asymmetry*, 2001, **12**, 2657; T. Inghardt, T. Frejd and G. Svensson, *Tetrahedron*, 1991, **47**, 6469.
6 Y. Dong, N. N. Pai, S. L. Ablaza, S.-X. Yu, S. Bolvig, D. A. Forsyth and P. W. Le Quesne, *J. Org. Chem.*, 1999, **64**, 2657.
7 D. Seebach and M. F. Züger, *Tetrahedron Lett.*, 1985, **25**, 2747.
8 G. Frater, *Helv. Chim. Acta*, 1979, **62**, 2825; D. Seebach and D. Wasmuth, *Helv. Chim. Acta*, 1980, **63**, 197.
9 L. E. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 597; L. A. Clizbe and L. E. Overman, *Org. Synth.*, 1978, **58**, 4.
10 (*a*) L. E. Overman, *J. Am. Chem. Soc.*, 1976, **98**, 2901; (*b*) L. E. Overman, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 579.
11 Representative procedure for the palladium catalysed rearrangements: The trichloroacetimidate **9** (1 mmol) was dissolved in THF (10 ml) under a nitrogen atmosphere and bis(benzonitrile)-palladium(II) chloride (10 mol%) was added. After 3 h, the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography, eluting with 20% diethyl ether in petroleum ether to give the rearranged products as a colourless oil.
12 U. Nubbemeyer, *Synthesis*, 2003, 961; R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
13 J. A. Marshall and A. W. Garofalo, *J. Org. Chem.*, 1993, **58**, 3675.
14 C. McKay, T. J. Simpson, C. L. Willis, A. K. Forrest and P. J. O'Hanlon, *Chem. Commun.*, 2000, 1109.